UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/381,747	09/22/99	TORMO M	UTSC:550---/

HM22/0710

DAVID L PARKER
ARNOLD WHITE & DURKEE
PO BOX 4433
HOUSTON TX 77210-2198

EXAMINER	
LACOURCIERE,K	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 07/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/381,747	Tormo et al.
Examiner	**Group Art Unit**
Karen A. Lacourciere	1635

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

2. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 08/726,211, filed 10-04-1996. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Non-initialed changes have been made to the address of inventor Tormo.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-20 of this application conflict with claims 1-41, 43-50, and 52-56 of Application No. 08/726,211. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

6. Claims 1-20 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-41, 43-50 and 52-56 of copending Application No. 08/726,211. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: An antisense oligonucleotide targeted to the initiation codon of bcl-2 mRNA, including SEQ ID NO:1, encapsulated in a liposome.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9 and 10 are indefinite due to the recitation "a second, bcl-2 encoding polynucleotide". Claims 1, 9 and 10 are unclear because they recite a second bcl-2 encoding polynucleotide without reciting a first bcl-2 encoding polynucleotide. Due to dependence on

claim 1, 9 or 10, claims 2-8 and 11-20 would be indefinite for the same reasons. As such, one skilled in the art would not know what methods and compositions claims 1-20 would encompass.

Claims 5-8 and 14 are indefinite due to the recitation "the lipid" because it refers back to claim 1, which recites two different lipids and it is unclear which lipid "the lipid" is referring to.

Claim 9 is indefinite due to the recitation "is active". It is unclear what activities the phrase "is active" is meant to impart to the promoter in the claimed composition. As such, one skilled in the art would not know what compositions claim 9 would encompass.

Claims 10-20 are drawn to methods of inhibiting the expression of a gene. Such methods are incomplete as there is no step in each method which relates back to the outcome set forth in the preamble. Therefore, claims 10-20 are indefinite.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10-20 are drawn broadly to inhibiting any disease associated with bcl-2 by administering an antisense oligonucleotide targeted to bcl-2 in a neutral liposome composition to a cell expressing bcl-2 and bax. Claims 10-20 are draw broadly to methods of treatment with any bcl-2 targeted antisense for any type of cancer cell in any organism, including human, for any neutral liposome composition.

The specification as filed provides one example wherein nude mice injected with follicular lymphoma cells were treated with a liposomal composition comprising antisense targeted to bcl-2, wherein some treated mice exhibit a reduction in proliferation of the injected lymphoma cells. Further, the specification, as filed, presents examples of in vitro (cell culture) treatment of cells using compositions which comprise a neutral liposome and bcl-2 targeted antisense wherein the viability of one cell line (Johnson follicular lymphoma) is decrease, but the viability of another bcl-2/bax expressing cell line (Raji Burkitt lymphoma cells) is not effected.

No examples are presented which demonstrate an inhibition of a disease state using compositions comprising neutral lipids and bcl-2 targeted antisense, nor is there any demonstration that the reduction of proliferation of injected lymphoma cells correlates with an effective treatment for follicular lymphoma or any other bcl-2 associated disease.

The specification indicates that in vitro treatment of cancer cells using a composition comprising a neutral lipid and antisense targeted to bcl-2 is unpredictable with respect to which cell types are responsive to treatment. The specification does not provide guidance which would allow one skilled in the art to determine what cell lines would respond in vivo, or in vitro, to a

composition comprising a neutral lipid and antisense targeted to bcl-2. Further, there is no evidence provided in the instant specification that inhibition of a cancer cell line in vitro using a composition comprising a neutral lipid and an antisense molecule targeted to bcl-2 would correlate with the inhibition of a disease state in vivo.

As per Agrawal, Branch and Crooke, the *in vivo* (whole organism) application of antisense without direct evidence is a highly unpredictable endeavor due to target accessibility and delivery issues. Delivery of an antisense oligonucleotide targeted to bcl-2 in vitro using a composition comprising a neutral lipid would not provide guidance for delivery of an antisense targeted to bcl-2 in vivo using a composition comprising a neutral lipid.

The specification as filed provides only one example wherein an antisense oligonucleotide targeted to bcl-2 is used to inhibit cancer cell growth in vivo. The disclosed model uses a human follicular cell line injected into an immunosuppressed mouse. It is well known in the art that mouse models, particularly when immunosuppressed mice are used, do not always correlate with therapeutic results in humans or other organisms (see Gura, Golden). "[M]ost drugs that work in lab animals tend to be duds in humans. The field is littered with "magic bullets" that failed....no more than 10% or 20% of agents tried in mice succeed"(see Golden). Xenograft models, human tumors in immunosuppressed mice, "don't behave like naturally occurring tumors in humans...drugs tested in xenografts appeared effective but worked poorly in humans" (see Gura, p 1041, second column). Further, "animals [xenograft mice] apparently do not handle the drugs exactly the way the human body does"(Gura). Delivery of antisense targeted to bcl-2 in a

xenograft mouse would not provide guidance to deliver the same antisense oligonucleotide to a human or any other mammal. Further, the mouse model presented does not demonstrate that a disease state is inhibited using the claimed method. There is no art recognized nexus disclosed between the mouse model presented and a disease state nor is there any evidence that results obtained in the disclosed mouse model would extend to any other organism, any other cell line, any other neutral lipid composition or any other bcl-2 targeted oligonucleotide.

Prophetic examples are provided for carrying out in vivo testing and treatment, however few details are provided.

Based on the broad breadth claimed, the unpredictability of the art of antisense, the unpredictability of the claimed methods demonstrated in vitro, the lack of correlating working examples, the lack of guidance provided by the inventor with respect to in vivo inhibition of a bcl-2 associated disease it would require undue trial and error experimentation for one skilled in the art to practice the methods of inhibiting a disease using a composition of a neutral lipid and a bcl-2 targeted antisense oligonucleotide as claimed.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Redd or Green et al. each in view of Tari et al.

Evan teaches the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein (p 7, lines 10-29), wherein the oligonucleotide is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 15, lines 16-23). Evan teaches that the antisense oligonucleotide can be synthesized from an expression construct encoding the antisense oligonucleotide (p 18, lines 26-30) and that the expression construct is preferably delivered via a liposome (p 59, lines 6-7).

Reed teaches an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of the bcl-2 protein (p 3, lines 2-22). The antisense oligonucleotide taught by Reed is preferably targeted to the translation initiation codon of bcl-2 and comprises SEQ ID NO:1 (p 13, lines 2-5). Reed teaches that the antisense oligonucleotide, or a vector which expresses the antisense oligonucleotide, is preferably delivered via a liposome (p 14, lines 16-25).

Green et al. teaches antisense oligonucleotides targeted to anti-apoptotic genes, including bcl-2 (column 3, lines 51-67) wherein said antisense oligonucleotides are preferably targeted to the translation initiation codon of the target gene (column 4, lines 46-51). Green et al. teach that the antisense oligonucleotides can be encapsulated into liposomes for administration (see for example column 6, lines 60-63) may be delivered using an expression vector encoding the antisense oligonucleotide (column 6, lines 8-10).

Evan, Reed and Green et al. do not teach a liposome composed of neutral lipids, nor do they teach liposomes composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, or dioleoylphosphatidylcholine.

Tari et al. teach antisense oligonucleotides encapsulated in a liposome comprised of neutral lipids, including liposomes composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, or, preferably, dioleoylphosphatidylcholine (see for example column 1, line 66- column 2, line 56).

It would have been obvious to one skilled in the art at the time the invention was made to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a lipid, as taught by Evan, Reed or Green et al., using the formulations taught by Tari et al. One skilled in the art would have been motivated to use the neutral lipid formulations taught by Tari et al. for the antisense oligonucleotide liposome compositions taught

by Evan, Reed or Green et al. because Tari et al. teach that liposome formulations comprised of neutral lipids, including dioleoylphosphatidylcholine, impart improved stability and cellular uptake to antisense oligonucleotides. Therefore, it would have been prima facie obvious to one skilled in the art at the time the instant invention was made to make a composition comprising the antisense oligonucleotides targeted to bcl-2 encapsulated in a liposome, as taught by Evan, Reed or Green using the liposome formulations taught by Tari et al., absent evidence to the contrary.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott can be reached at (703) 308-4003. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

Karen A. Lacourciere

July 3, 2000